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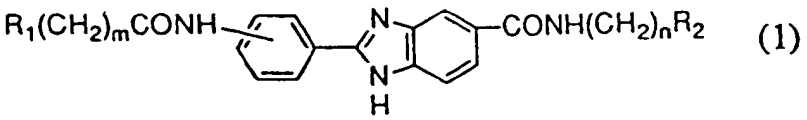
(71) Applicant: **MITSUI TOATSU CHEMICALS, INC.**
Tokyo (JP)

(72) Inventors:
- **Matsunaga, Akio**
  Mobara-shi, Chiba-ken (JP)
- **Nakajima, Yuki**
  Mobara-shi, Chiba-ken (JP)
- **Kohno, Hiroshi**
  Mobara-shi, Chiba-ken (JP)
- **Ohkouchi, Hiroshi**
  Mobara-shi, Chiba-ken (JP)
- **Iwata, Daiji**
  Mobara-shi, Chiba-ken (JP)
- **Edatsugi, Hajime**
  Mobara-shi, Chiba-ken (JP)

(74) Representative: **VOSSIUS & PARTNER**
Siebertstrasse 4
81675 München (DE)

(54) Phenylbenzimidazole derivatives

(57) An anticancer agent, an antiviral agent or an antimicrobial agent which contains, as an active ingredient for acting on DNA, a compound presented by the following formula (1) or its pharmacologically acceptable salt:



(1)

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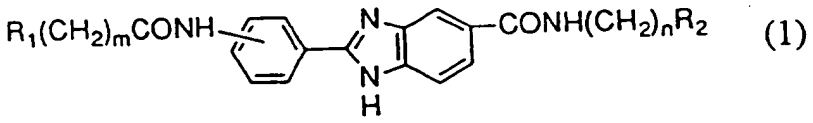
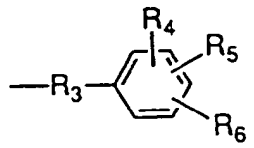


(1)

wherein each of m and n is independently an integer of from 0 to 5; each of R_1 and R_2 is independently a hydrogen atom, a halogen atom, an alkylthio group having 1 to 8 carbon atoms, preferably 1 to 4 carbon atoms, an amino group which may be substituted, an ammonium group which may be substituted, a sulfonium group which may be substituted, a phenyl group which may be substituted, a hetero-five-membered ring group which may be substituted, a hetero-six-membered ring group which may be substituted, an amidino group, a guanidino group, an amino acid residue or a group represented by the formula (2)



(2)

wherein R_3 is a direct bond or an oxygen atom {when R_3 is an oxygen atom, m or n of $(CH_2)_m$ or $(CH_2)_n$ to which R_3 bonds is not 0}; R_4 is a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, an alkoxy group having 1 to 8 carbon atoms, a halogen atom, a trifluoromethyl group, a cyano group, an amidino group, a carboxyl group or $-COR_7$ wherein R_7 is an alkylamino group having 1 to 8 carbon atoms which may be substituted by a substituted amino group, an amino group which may be substituted by a phenyl group which may be substituted, or a benzylamino group which may be substituted; R_5 is a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, an alkoxy group having 1 to 8 carbon atoms or a halogen atom; R_6 is a $-(CH_2)_pN(R_8)_2$ or $-(CH_2)_pNR_8R_9$ wherein p is an integer of from 0 to 5; R_8 is $-CH_2CH_2W$ wherein W is a halogen atom, a hydroxyl group, a mesyloxy group or a tosyloxy group or $-OCOR_7$ wherein R_7 is as defined above; R_9 is an alkyl group having 1 to 5 carbon atoms or a mesyl group; and the phenyl group in formula (1) having a $R_1(CH_2)_mCONH$ group can be substituted by the $R_1(CH_2)_mCONH$ group at any position, preferably at the 3-position or the 4-position of the phenyl group.

The compound of the present invention acts on DNA, and so it is useful as an active ingredient of an anticancer agent, an antiviral agent or an antimicrobial agent.

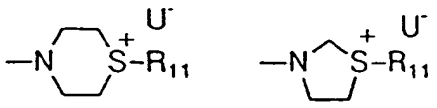
Now, the present invention will be described in more detail.

In formula (1), examples of "a halogen atom" represented by R_1 or R_2 include Cl, Br and I.

Examples of "an amino group which may be substituted" represented by R_1 or R_2 include an amino group, monoalkylamino groups and dialkylamino groups substituted by a straight-chain or a branched alkyl group having 1 to 8 carbon atoms. As the dialkylamino groups, those having the alkyl groups of 1 to 4 carbon atoms are desirable. Above all, a methylamino group, ethylamino group, n-propylamino group, isopropylamino group, n-butylamino group, dimethylamino group, diethylamino group, dipropylamino group and diisopropylamino group are desirable.

Examples of "an alkylthio group having 1 to 8 carbon atoms" represented by R_1 or R_2 include straight-chain and branched alkylthio groups having 1 to 8 carbon atoms, and typical suitable examples thereof include a methylthio group, ethylthio group, n-propylthio group, isopropylthio group, n-butylthio group, isobutylthio group, t-butylthio group, n-pentylthio group, n-hexylthio group, n-heptylthio group and n-octylthio group.

Examples of "an ammonium group which may be substituted" represented by R_1 or R_2 include a trimethylammonium group, a triethylammonium group and ammonium groups represented by the following formulae (3-1) to (3-14):



(4-1) (4-2)

The acid residue bound to the above "sulfonium group which may be substituted" is required to be usable as a portion of drug, and examples of the acid residue include inorganic acid residues such as hydrogen chloride, hydrogen iodide, hydrogen bromide, tetrafluoroboric acid, perchloric acid and phosphoric acid, organic sulfonic acid residues such as methanesulfonic acid, toluenesulfonic acid, camphorsulfonic acid and 1,5-naphthalenedisulfonic acid, and carboxylic acids such as lactic acid, maleic acid and malonic acid. In these formulae, R_{11} is a straight-chain or a branched alkyl group having 1 to 8 carbon atoms, and suitable examples thereof include a methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, t-butyl group, n-pentyl group, n-hexyl group, n-heptyl group and n-octyl group.

Examples of "a phenyl group which may be substituted" represented by R_1 or R_2 include a phenyl group which may be substituted with at least one of halogen atoms (a fluorine atom, a chlorine atom, a bromine atom and an iodine atom), straight-chain and branched alkyl groups having 1 to 5 carbon atoms, straight-chain and branched alkoxy groups having 1 to 3 carbon atoms, alkoxycarbonyl groups having 2 to 4 carbon atoms, a trifluoromethyl group, a cyano group, an amidino group, a guanidino group and dialkylamino groups in which the alkyl groups have 1 to 3 carbon atoms, respectively. Suitable examples thereof include a chlorophenyl group, dichlorophenyl group, trichlorophenyl group, bromophenyl group, dibromophenyl group, tribromophenyl group, fluorophenyl group, difluorophenyl group, trifluorophenyl group, methylphenyl group, ethylphenyl group, n-propylphenyl group, isopropylphenyl group, n-butylphenyl group, isobutylphenyl group, t-butylphenyl group, n-pentylphenyl group, methoxyphenyl group, ethoxyphenyl group, n-propyloxyphenyl group, isopropyloxyphenyl group, methoxycarbonylphenyl group, ethoxycarbonylphenyl group, n-propyloxycarbonylphenyl group, trifluoromethylphenyl group, cyanophenyl group, amidinophenyl group, guanidinophenyl group, dimethylaminophenyl group, diethylaminophenyl group, dipropylaminophenyl group, methoxyphenyl group and 3,4,5-trimethoxy group. In the case of monosubstition, the position of the substituent on the phenyl group is the 2-, 3- or 4-position; in the case of disubstitution, the positions of the substituents thereon are two positions of the 2-, 3-, 4-, 5- and 6-positions; and in the case of trisubstitution, the positions of the substituents thereon are three positions of the 2-, 3-, 4-, 5- and 6-positions, unless otherwise noted.

Examples of "a hetero-five-membered ring group which may be substituted" represented by R_1 or R_2 include a pyrrolyl group, furyl group, thienyl group, imidazolyl group, oxazolyl group, pyrazolyl group, thiazolyl group, isothiazolyl group, isoxazolyl group, pyrrolinyl group, imidazolidinyl group, pyrazolidinyl group, pyrazolinyl group, furazanyl group, tetrahydrofuranyl group, triazolyl group and tetrazoyl group.

Examples of "a hetero-six-membered ring group which may be substituted" represented by R_1 or R_2 include a pyridyl group, pyrimidinyl group, pyranyl group, pyrazinyl group, pyridazinyl group, piperidyl group, piperazinyl group, thiomorpholino group, 4-methyl-1-piperazino group, 4-benzyl-1-piperazino group, 1-morpholino group, 1-piperidino group, 4-piperidino group and 4-methyl-1-piperidino group.

Here, in the above-mentioned "a hetero-five-membered ring group which may be substituted" and "a hetero-six-membered ring group which may be substituted", the passage "may be substituted" means that this group may be substituted by, for example, a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom), a straight-chain and branched alkyl group having 1 to 5 carbon atoms, a straight-chain and branched alkoxy group having 1 to 5 carbon atoms, an alkoxycarbonyl group having 2 to 4 carbon atoms, a haloalkyl group having 1 to 3 carbon atoms, a cyano group, an amidino group and/or a dialkylamino group having 1 to 3 carbon atoms.

"An amino acid residue" as R_1 or R_2 is defined specially in the present invention as a group which can be obtained by omitting a carboxyl group from an amino acide. Suitable examples of this amino acid include arginine, histidine and lysine.

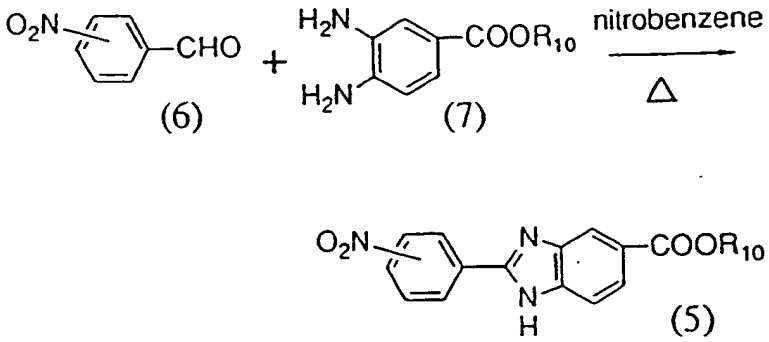
"A direct bond" represented by R_3 means that the substituted or non-substituted phenyl group in the formula (2) is directly bonded via no R_3.

Examples of a halogen atom represented by R_4 or R_5 in the formula (2) include F, Cl, Br and I.

Suitable examples of a halogen atom of W in $-CH_2CH_2W$ represented by R_8 include Cl and Br.

Preferable examples of an alkyl group having 1 to 8 carbon atoms represented by R_4 or R_5 include a methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, t-butyl group, n-pentyl group, n-hexyl group, n-heptyl group and n-octyl group.

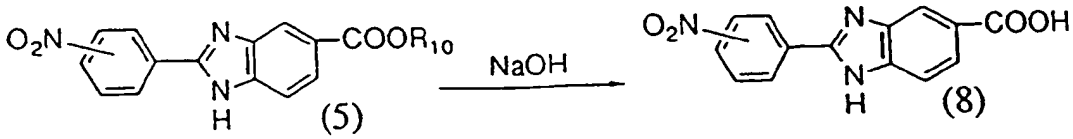
Reaction formula (1):



Reaction formula (1)

Here, when the ester is obtained, this ester can be hydrolyzed as shown in the following reaction formula (2), thereby obtaining a 1H-2-phenylbenzimidazole-5-carboxylic acid derivative represented by formula (8):

Reaction formula (2):



Reaction formula (2)

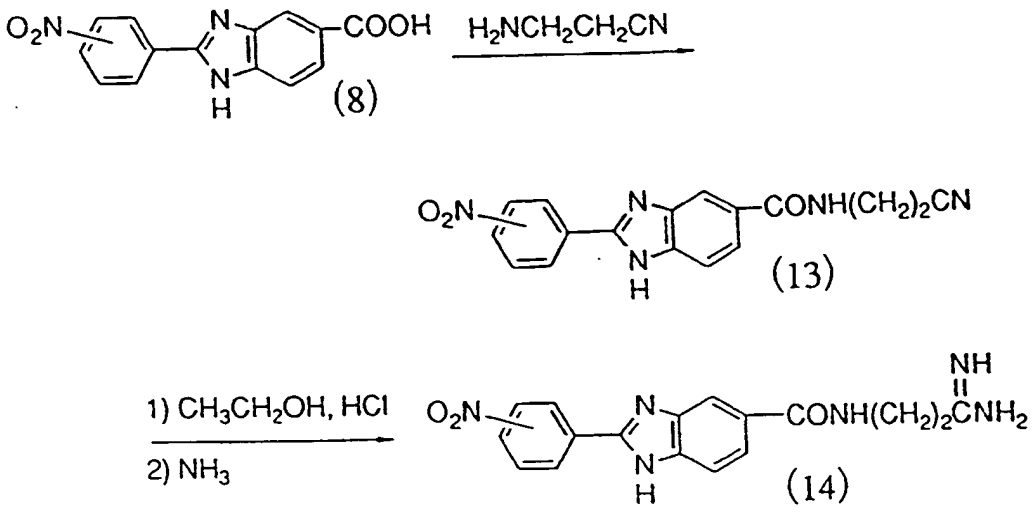
No particular restriction is put on the amounts of the aldehyde of formula (6) and the 3,4-diaminobenzoic acid ester of formula (7), but in general, the amount of the latter is in the range of from 80 to 120 mol parts with respect to 100 mol parts of the former. The reaction in nitrobenzene is carried out by heating, until the starting materials have disappeared, while the progress of the reaction is observed, but in either case, a heating time of 5 to 100 hours leads to successful results. The heating may be carried out continuously or intermittently, but the total heating time should be in the above-mentioned range. The hydrolysis of the ester can be accomplished by heating the ester in the presence of sodium hydroxide or potassium hydroxide in a mixed solvent of water and ethanol or water and methanol. In this case, the ratio of water is in the range of from 5 to 90% by weight, preferably from 40 to 60% by weight.

The heating temperature is in the range of from 50°C to a reflux temperature.

Concretely, if 3-nitrobenzaldehyde or 4-nitrobenzaldehyde is selected as the starting material, 1H-2-(3-nitrophenyl)benzimidazole-5-carboxylic acid or 1H-2-(4-nitrophenyl)benzimidazole-5-carboxylic acid can be synthesized by the same procedure as described above. The compound represented by the formula (8) can be used for the synthesis of compounds in the groups A and B.

Next, this reaction mixture is suspended in ethanol, and a hydrogen chloride gas is then fed. Afterward, the resultant crystal is collected by filtration, and then dissolved or suspended in a solvent. Ammonia gas is further introduced into the solution to obtain a desired amidino compound represented by formula (14). In this case, the solvent is preferably ethanol or a mixed solvent of ethanol and methanol. In the mixed solvent, the ratio of ethanol can optionally be selected in the range of from 10 to 100%. If this amidino compound is used as the compound of formula (10) in reaction formula (3), the compound of the group A in which R_2 is an amidino group can be obtained:

Reaction formula (4):



Reaction formula (4)

Typical examples of the compound of formula (8) in the reaction formulae (3) and (4) include 1H-2-(3-nitrophenyl)benzimidazole-5-carboxylic acid or 1H-2-(4-nitrophenyl)benzimidazole-5-carboxylic acid.

Next, reference will be made to a synthesis method of a compound in which R_1 is a desired group.

For example, a compound in which R_1 is a substituent represented by formula (2) can be synthesized by a process shown by the following reaction formula (5):

to 30°C. During the reaction, the progress of the reaction can be observed, but the reaction time is usually in the range of from 1 to 50 hours. Alternatively, the compound of formula (19) can be treated with thionyl chloride or oxalyl chloride in a usual solvent (e.g., methylene chloride, chloroform, toluene and DMF can be used singly or in the form of a mixture of two or more thereof) to obtain an acid chloride, and this product can be then reacted with the compound represented by formula (11) to bond them to each other. Here, the reaction is preferably carried out in the range of from -5 to 30°C. During the reaction, the progress of the reaction can be observed, but the reaction time is usually in the range of from 1 to 50 hours.

Another side chain represented by R_1 can also be prepared by using commercially available reagents and several steps of known reactions.

III. Synthesis of a compound in the group B

First, a technique of introducing R_2 will be described.

To start with, reference will be made to the synthesis of a compound in which R_2 is, for example, a substituent represented by formula (2).

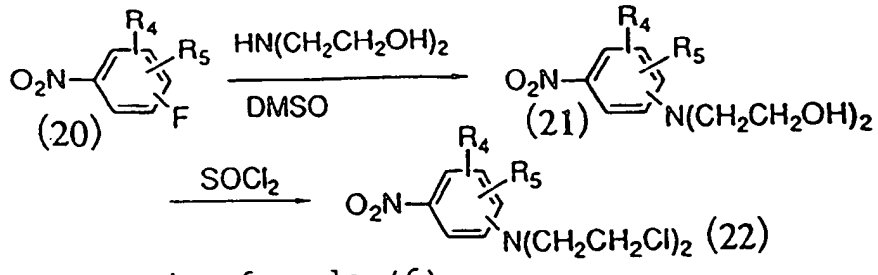
The introduction of R_6 into the substituent represented by formula (2) can usually be achieved by each of the following two methods.

Method A:

As shown in the following reaction formula (6), a halogenated benzene derivative (in formula (20), F is shown as an example of a halogen atom) containing a nitro group and suitable substituents which is represented by formula (20) is reacted with N,N-bis(2-hydroxyethyl)amine to obtain a compound of formula (21). In this time, DMSO is used as a solvent, and the reaction temperature is in the range of from 20 to 150°C. The reaction time is preferably in the range of from 30 minutes to 10 hours. As the halogenated benzene derivative containing the suitable substituents, there can be used a commercially available reagent or a compound which can be synthesized by the use of a known reaction. For example, the halogenated benzene derivative containing an amidino group can be introduced from a halogenated benzene derivative containing a cyano group by the utilization of a known reaction.

Next, the thus obtained intermediate of formula (21) is reacted with a suitable chlorinating agent such as thionyl chloride, oxalyl chloride, phosphorus pentachloride, phosphorus oxychloride, mesyl chloride or a combination of mesyl chloride (in DMF) and sodium chloride to obtain a chloride of formula (22). The reaction is carried out at 0 to 150°C, and a reaction time is in the range of from 5 minutes to 5 hours. As a solvent, there can be used a usual solvent such as chloroform, benzene or toluene. Furthermore, such a solvent can be mixed with DMF. In addition, the reaction can be carried out without solvent.

Reaction (6):



Reaction formula (6)

Method B:

As shown in the following reaction formula (7), an aniline derivative (in the case that p is 0) or an aminoalkylbenzene derivative (in the case that p is 1 or more) having a nitro group and suitable substituents which is represented by formula (23) is reacted with ethylene oxide to obtain a compound of formula (24). As a solvent at this time, there can be used a

For the synthesis of the corresponding amino compound from the usual nitrobenzene derivative, there is usually employed the catalytic hydrogenation using Pd/C as a catalyst or a process utilizing a reaction in which tin chloride and hydrochloric acid are used. In particular, as the reduction method of the above-mentioned nitrobenzene derivative to which N,N-bis(2-chloroethyl)amino group is bonded, there is known a reduction method using tin chloride and hydrochloric acid, as reported in, for example, J. Chem. Soc. p. 1972-1983 (1949) or J. Med. Chem. Vol. 33, p. 112 to 121 (1990).

However, in place of this usual method, the following technique can also be used to efficiently perform the reduction reaction, and some treatments subsequent to the reaction can easily be accomplished advantageously. That is to say, the nitro compound which is the starting material is dissolved in a suitable solvent, for example, a single solvent or a mixed solvent of ethanol, methanol, ethyl acetate, THF and DMF, and Pd/C is then added in an amount corresponding to 0.5 to 50% by weight of the nitro compound, followed by hydrogenation at room temperature under atmospheric pressure, to obtain the corresponding amino compound. At this time, hydrochloric acid can be added in an amount equal to or more than mols of the nitro compound, usually in an amount of from 1 to 1.2 mols. The catalyst is removed by filtration and the solvent is then distilled off, followed by a treatment with one or more kinds of suitable solvents such as ethanol, IPA and ether, whereby a desired hydrochloride can be simply obtained.

Furthermore, as shown in the following reaction formula (9), an amino compound of formula (28) can be synthesized from a carboxylic acid of formula (27) in accordance with a process shown in J. Med. Chem. Vol. 33, p. 3014-3019 (1990).

Reaction formula (9):

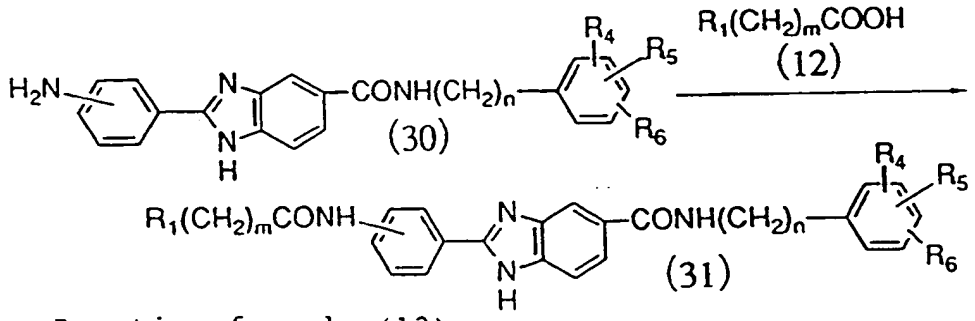
Reaction formula (9)

By the use of this process, an aminoalkylbenzene derivative can be synthesized in which R_3 is a chain having two or more methylene groups.

Here, the compound of formula (26) corresponds to the compound of formula (28) in which n is 0 and R_6 is an N,N-bis(2-chloroethyl)amino group. In the following description, therefore, reactions using the compound having formula (28) will be referred to, but needless to say, the compound of formula (26) can be used as the compound of formula (28).

As shown in the reaction formula (10), a benzimidazole derivative of formula (8) is bonded to the amino compound of formula (28) in the presence of a usual condensing agent (CDI, DECP, DCC, a combination of DCC and HOBt, or the like) to synthesize the compound of formula (29).

Reaction formula (12):



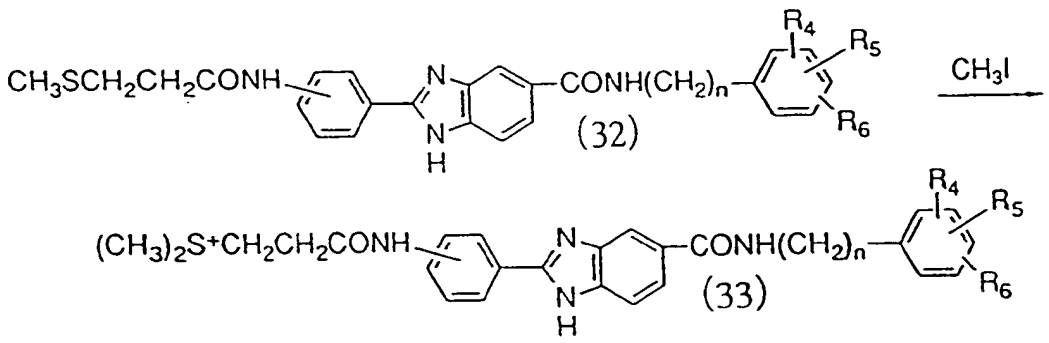
Reaction formula (12)

As a solvent for this reaction, a usual solvent is usable, but DMF or a mixed solvent containing DMF is preferred. The reaction is preferably carried out at a temperature of from 0 to 40°C for a period of from 30 minutes to 40 hours.

The employment of the following process permits the synthesis of a compound in the group B in which R_1 is a hydrogen atom, a halogen atom or a group other than the groups represented by formula (2).

For example, as shown in the following reaction formula (13), a compound represented by formula (32) can be methylated in accordance with a technique described in J. Org. Chem., Vol. 25, p. 804-807 (1960) or with the aid of a usual methylating agent (e.g., methyl iodide, dimethylsulfuric acid or methyl p-toluenesulfonate) to obtain a sulfonium derivative represented by formula (33).

Reaction formula (13):



Reaction formula (13)

As a solvent for this reaction, formic acid, acetic acid, acetone or the like can be used. Alternatively, the reaction can be carried out without solvent. The reaction is preferably carried out at a temperature of from 0 to 60°C for a period of from 1 to 60 hours.

A counter anion (I^-) of the sulfonium compound obtained here can be converted into another anion in a known manner. For example, I^- can be converted into Cl^- by the use of a Cl^- type ion exchange resin (Dowex 1x8).

In the above-mentioned reaction formula (12), when a compound in which R_1 is a substituted or an unsubstituted amino group is used as the compound of formula (12), a compound in the group B can be obtained in which R_1 is the substituted or the unsubstituted amino group.

The thus obtained compound in which R_1 is the amino group substituted by two alkyl groups is further alkylated in a known manner, whereby this compound can be converted into a compound in which R_1 is an ammonium group.

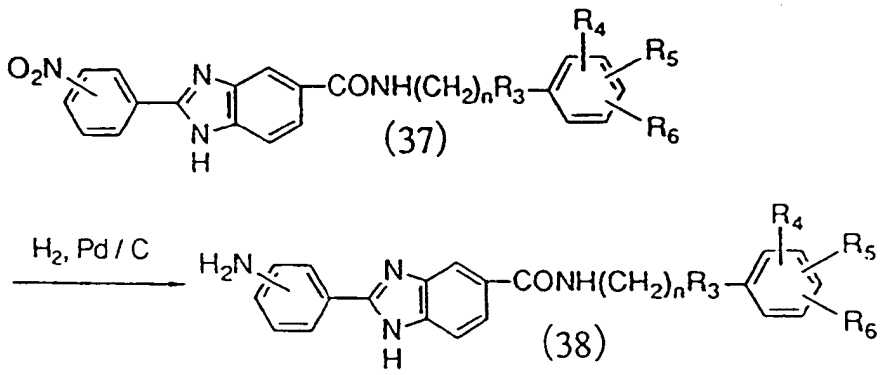
this case, the reaction is preferably carried out at a temperature of from 0 to 40°C for a period of from 30 minutes to 24 hours.

Another compound can be synthesized by changing starting materials under the above-mentioned conditions.

The compounds in the groups A and B can be synthesized as described above, but the synthesis of a compound in which both of R_1 and R_2 are groups represented by formula (2) can be accomplished, for example, as follows.

In the first place, as shown in the following reaction formula (16), a compound (a nitro compound) represented by formula (37) can be reduced to a corresponding amino group of formula (38) by catalytic hydrogenation using Pd/C as a catalyst. In this case, ethanol, methanol and DMF can be used singly or in a combination of two or more thereof as a solvent.

Reaction formula (16):



Reaction formula (16)

At this time, hydrochloric acid can be added in an amount equal to or more than mols of the nitro compound, usually in an amount of from 1 to 1.2 mols. The reaction is preferably carried out for a period of from 10 minutes to 20 hours.

Next, as shown in the following reaction formula (17), the amino compound of formula (38) can be reacted with a carboxylic acid derivative of formula (39) to obtain a compound represented by formula (40).

starch, cacao butter, hardened vegetable oil, kaolin and talc; binders such as powdered acacia, powdered tragacanth and gelatin; and disintegrators such as carboxymethylcellulose calcium and agar.

The capsules can be prepared in accordance with a usual procedure, i.e., by mixing a compound as an active ingredient with any of the previously enumerated carriers, and then filling the resulting mixture into hard gelatin capsules, soft capsules or the like.

In preparing the pharmaceutical compositions in the form of the injections, solutions, emulsions or suspensions diluents are used. Examples of the diluents which can often be used in this field include water, ethanol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, cotton seed oil, corn oil, peanut oil and olive oil. Moreover, the compounds of the present invention can also be used in the form of aqueous suspensions prepared by adding water thereto in the presence of a suitable surfactant, or in the form of emulsions prepared with the aid of a surfactant such as polyoxyethylene hardened castor oil (HCO-60). Furthermore, sodium chloride, glucose and/or glycerol may be contained in the pharmaceutical compositions, and a usual solubilizer, buffering agent and/or smoothing agent may be added thereto.

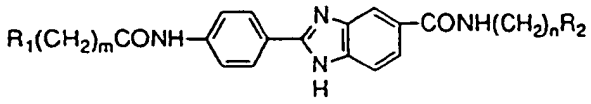
In preparing the pharmaceutical compositions in the form of suppositories, there can be used a wide variety of carriers which have been heretofore well known in this field. Examples of the carriers include polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin and semisynthetic glycerides.

If necessary, the pharmaceutical compositions can contain colorants, preservatives, perfumes, flavors, sweeteners and/or other drugs.

No particular restriction is put on an administration manner of the pharmaceutical compositions of the present invention, and they may be administered in accordance with the form of the pharmaceutical composition, the age, sex and other conditions of a patient and the severity of a disease. For example, the tablets, pills, solutions, suspensions, emulsions, powders, granules, syrups and capsules can be orally administered. The injections can be intravenously administered alone or after being mixed with a usual infusion fluid such as glucose or an amino acid. Alternatively, they may also be administered intramuscularly, subcutaneously or intraperitoneally as required. The suppositories can be administered intrarectally. The dose of the pharmaceutical compositions of the present invention can be suitably determined in compliance with the administration manner, the age, sex and other conditions of a patient, and the severity of a disease. However, the dose should usually be determined so that the amount of the compound as the active ingredient may be in the range of from about 0.001 to 1,000 mg per day for an adult. Moreover, it is desirable that each unit dosage form of the pharmaceutical composition to be administered contains the compound as the active ingredient in an amount in the range of about 0.001 to 1,000 mg.

Generally speaking, anticancer agents, for example, even agents such as adriamycin and cisplatin which have often been used, have no small side effect. At a present technical level, the side effect should be judged in consideration of relations with functional strength, and the problem of the side effect is unavoidable to some extent. The side effect of the compounds according to the present invention is at such a level as to be acceptable as the anticancer agents.

Table 1 (2)



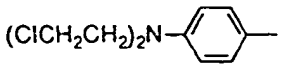
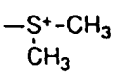
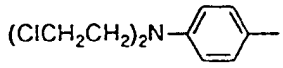
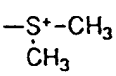
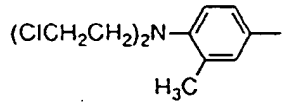
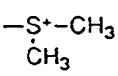
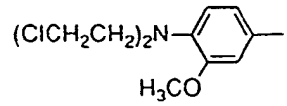
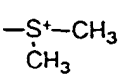
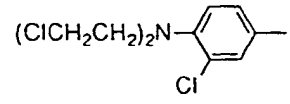
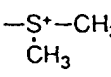
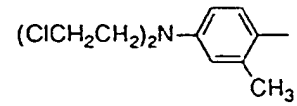
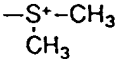
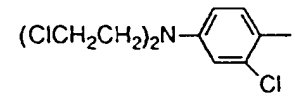
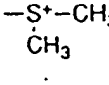
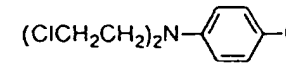
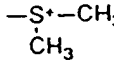
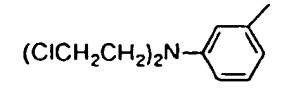
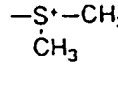
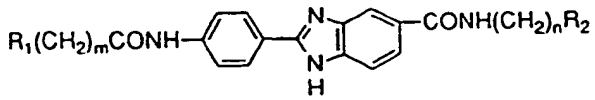
Compound No.	R_1	m	R_2	n
10		0		2
11		3		2
12		0		2
13		0		2
14		0		2
15		0		2
16		0		2
17		1		2
18		0		2

Table 1 (4)



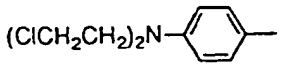
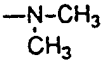
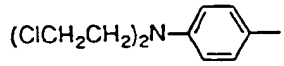
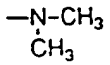
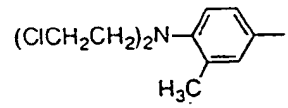
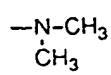
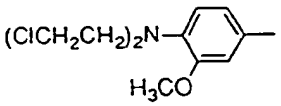
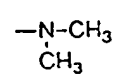
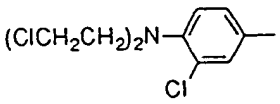
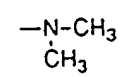
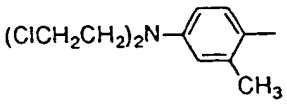
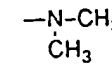
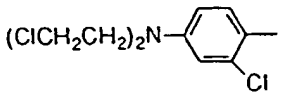
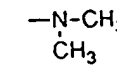
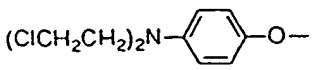
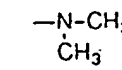
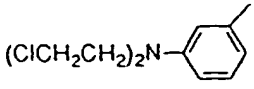
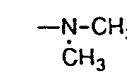
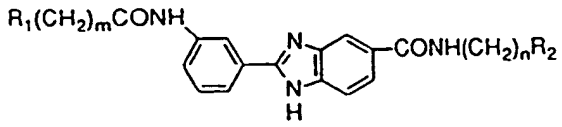
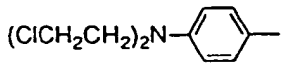
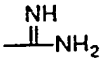
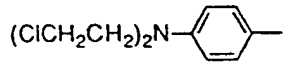
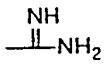
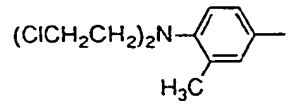
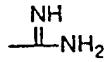
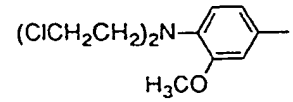
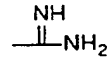
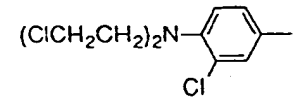
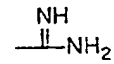
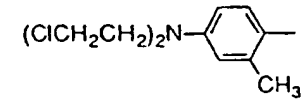
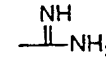
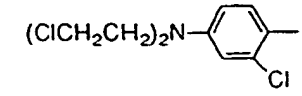
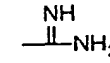
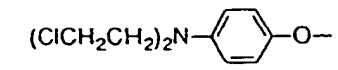
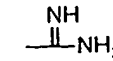
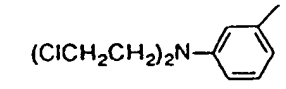
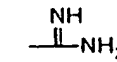
Compound No.	R_1	m	R_2	n
28		0		3
29		3		3
30		0		3
31		0		3
32		0		3
33		0		3
34		0		3
35		1		3
36		0		3

Table 1 (6)



Compound No.	R_1	m	R_2	n
46		0		2
47		3		2
48		0		2
49		0		2
50		0		2
51		0		2
52		0		2
53		1		2
54		0		2

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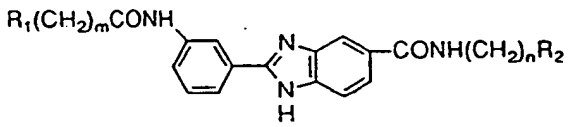
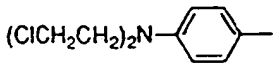
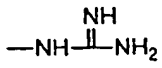
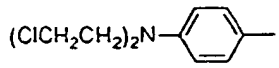
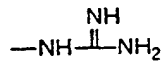
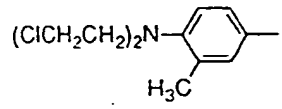
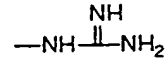
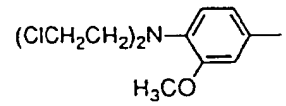
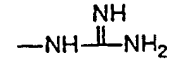
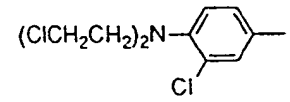
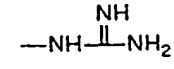
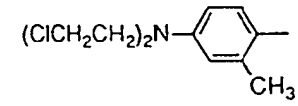
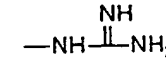
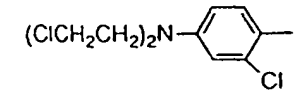
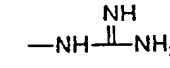
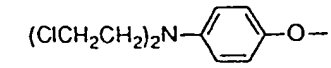
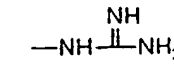
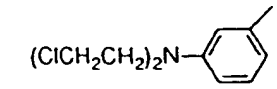
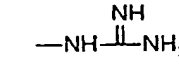


Compound No.	R_1	m	R_2	n
64		0		1
65		3		1
66		0		1
67		0		1
68		0		1
69		0		1
70		0		1
71		1		1
72		0		1

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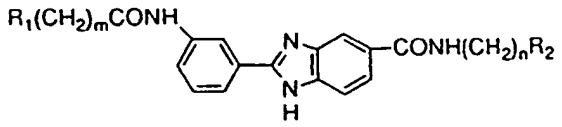


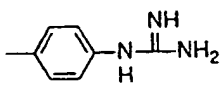
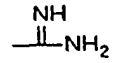
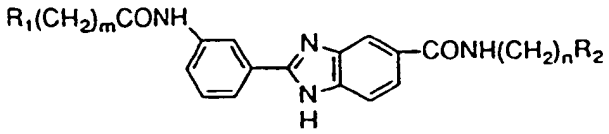
Compound No.	R_1	m	R_2	n
82	$(ClCH_2CH_2)_2N$—	0	—Cl	2
83	$(ClCH_2CH_2)_2N$—	0	—Br	2
84	$(ClCH_2CH_2)_2N$—	0	$-S-CH_3$	2
85	$(ClCH_2CH_2)_2N$—	0	$-\overset{CH_3}{\overset{+}{N}}-CH_3$ (CH3)	3
86	$(ClCH_2CH_2)_2N$—	0		3
87	$(ClCH_2CH_2)_2N$—	0		0
88	$(ClCH_2CH_2)_2N$—	0		0
89	H	0	$-\overset{CH_3}{N}-CH_3$	3
90	H	0		2

Table 1 (12)



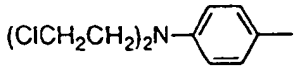
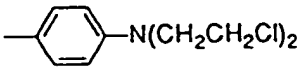
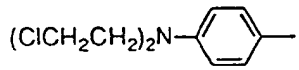
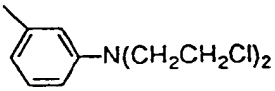
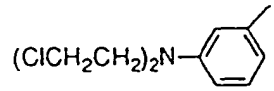
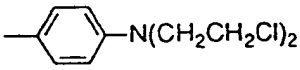
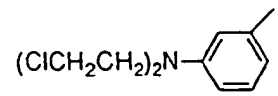
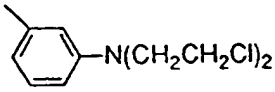
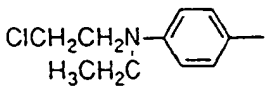
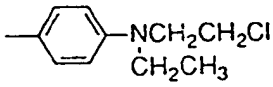
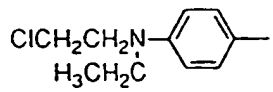
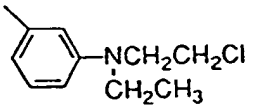
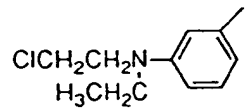
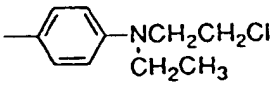
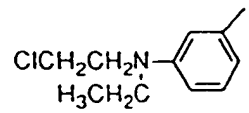
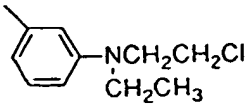
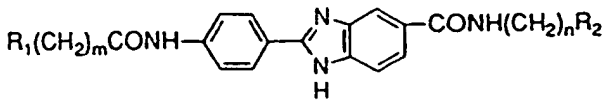
Compound No.	R_1	m	R_2	n
99		0		0
100		0		0
101		0		0
102		0		0
103		0		0
104		0		0
105		0		0
106		0		0

Table 1 (14)



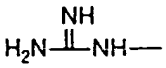
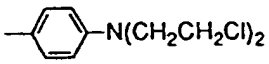
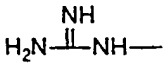
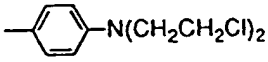
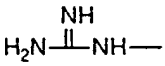
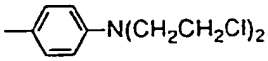
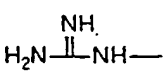
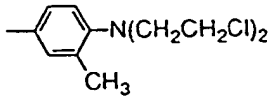
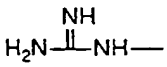
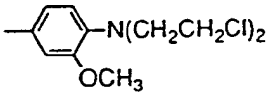
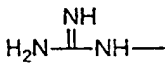
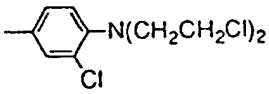
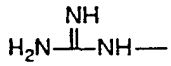
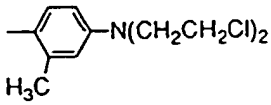
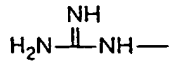
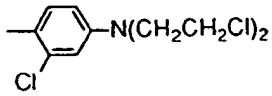
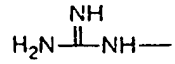
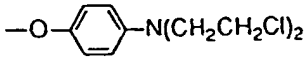
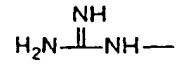
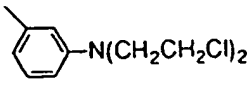
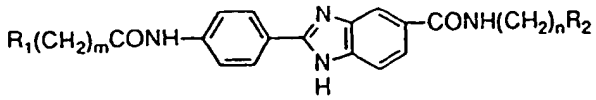
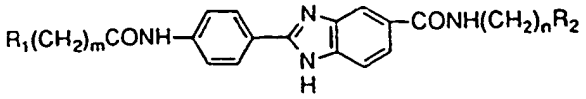
Compound No.	R_1	m	R_2	n
1011		3		0
1012		3		2
1013		3		3
1014		3		0
1015		3		0
1016		3		0
1017		3		0
1018		3		0
1019		3		1
1020		3		0

Table 1 (16)



Compound No.	R_1	m	R_2	n
1031	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$	0
1032	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$	2
1033	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$	3
1034	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$, CH_3	0
1035	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$, OCH_3	0
1036	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$, Cl	0
1037	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$, H_3C	0
1038	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$, Cl	0
1039	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-O-N(CH_2CH_2Cl)_2$	1
1040	$H_3C-\overset{CH_3}{\underset{}{N}}-$	3	$-N(CH_2CH_2Cl)_2$, CH_3	0

Table 1 (18)



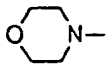
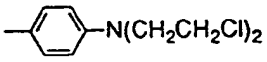
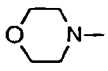
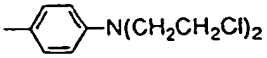
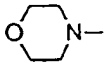
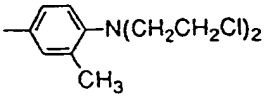
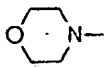
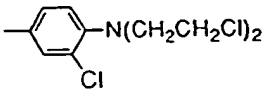
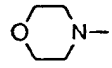
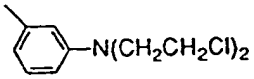
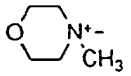
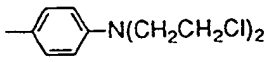
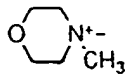
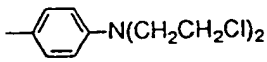
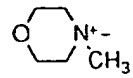
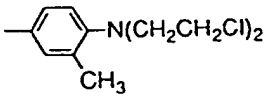
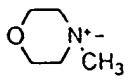
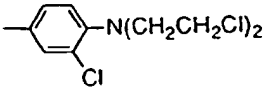
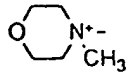
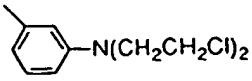
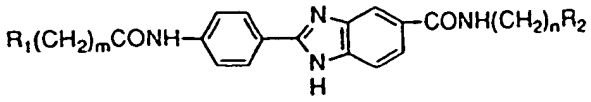
Compound No.	R_1	m	R_2	n
1051		2		0
1052		2		3
1053		2		0
1054		2		0
1055		2		0
1056		2		0
1057		2		3
1058		2		0
1059		2		0
1060		2		0

Table 1 (20)



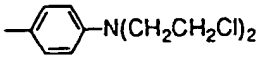
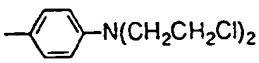
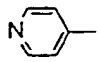
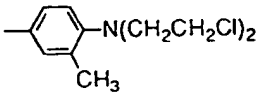
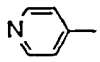
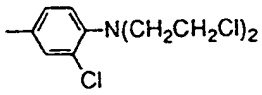
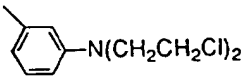
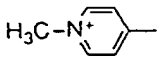
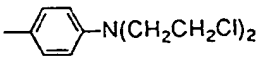
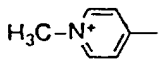
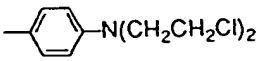
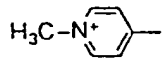
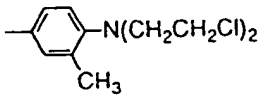
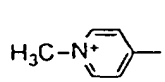
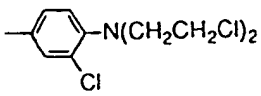
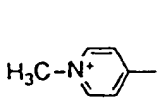
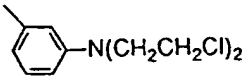
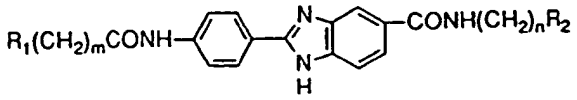
Compound No.	R_1	m	R_2	n
1071		1		0
1072		1		3
1073		1		0
1074		1		0
1075		1		0
1076		1		0
1077		1		3
1078		1		0
1079		1		0
1080		1		0

Table 1 (22)



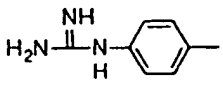
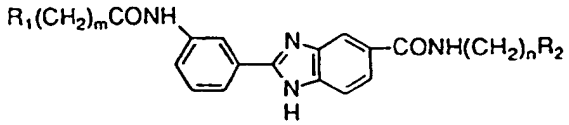
Compound No.	R_1	m	R_2	n
1091	H_3C-S—	2	—$N(CH_2CH_2Cl)_2$	0
1092	H_3C-S—	2	—$N(CH_2CH_2Cl)_2$ (CH_3)	0
1093	H_3C-S—	2	—$N(CH_2CH_2Cl)_2$ (Cl)	0
1094	Cl—	2	—$N(CH_2CH_2Cl)_2$	0
1095	N—	2	—$N(CH_2CH_2Cl)_2$	0
1096	N^+-CH_3	2	—$N(CH_2CH_2Cl)_2$	0
1097	H_3C-N^+(CH_3)(CH_3)-	3	—$N(CH_2CH_2Cl)_2$	0
1098		3	—$N(CH_2CH_2Cl)_2$	0
1099		0	—$N(CH_2CH_2Cl)_2$	0
1100		0	—$N(CH_2CH_2Cl)_2$	0

Table 1 (24)



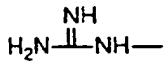
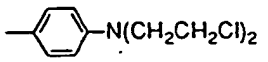
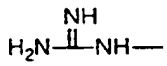
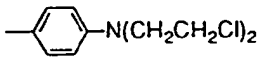
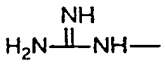
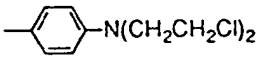
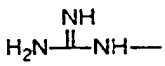
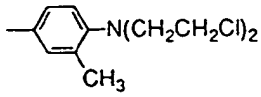
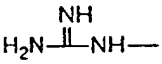
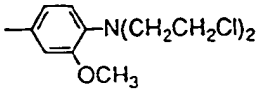
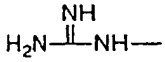
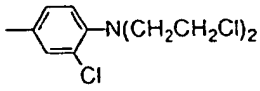
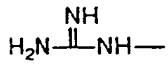
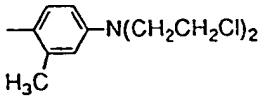
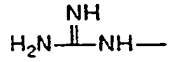
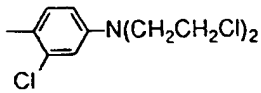
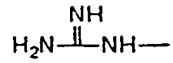
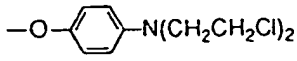
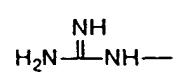
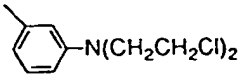
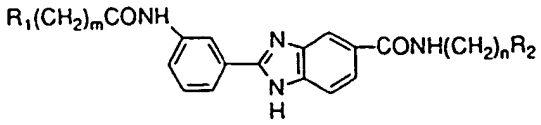
Compound No.	R_1	m	R_2	n
2001		1		0
2002		1		2
2003		1		3
2004		1		0
2005		1		0
2006		1		0
2007		1		0
2008		1		0
2009		1		1
2010		1		0

Table 1 (26)



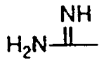
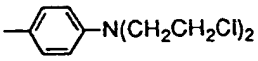
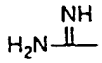
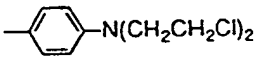
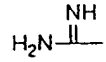
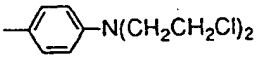
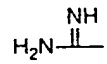
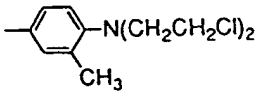
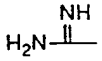
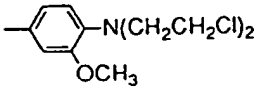
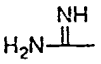
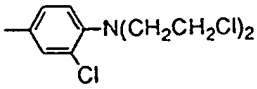
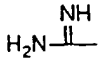
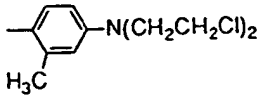
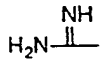
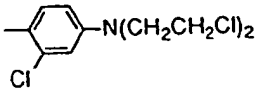
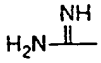
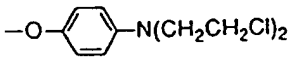
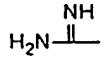
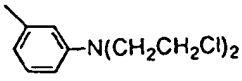
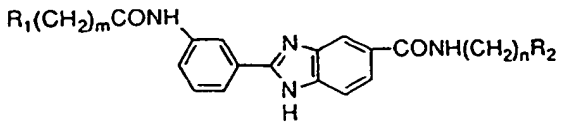
Compound No.	R_1	m	R_2	n
2021		3		0
2022		3		2
2023		3		3
2024		3		0
2025		3		0
2026		3		0
2027		3		0
2028		3		0
2029		3		1
2030		3		0

Table 1 (28)



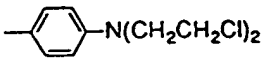
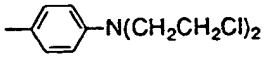
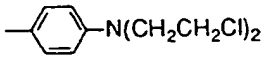
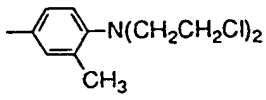
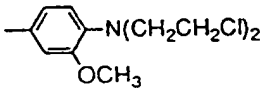
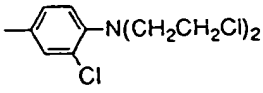
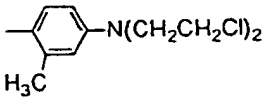
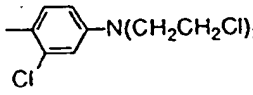
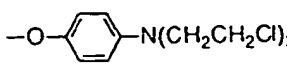
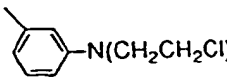
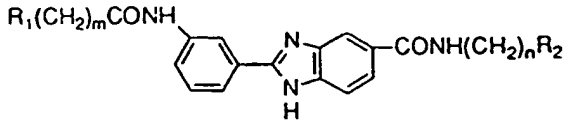
Compound No.	R_1	m	R_2	n
2041	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0
2042	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		2
2043	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		3
2044	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0
2045	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0
2046	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0
2047	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0
2048	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0
2049	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		1
2050	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	2		0

Table 1 (30)



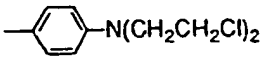
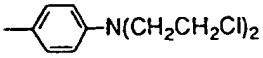
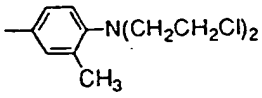
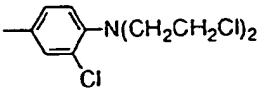
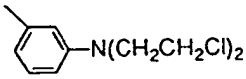
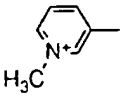
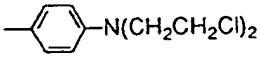
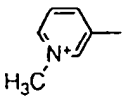
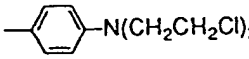
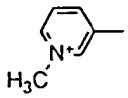
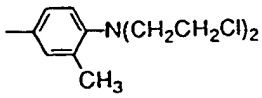
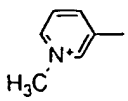
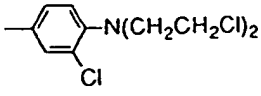
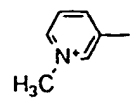
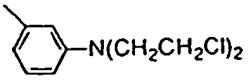
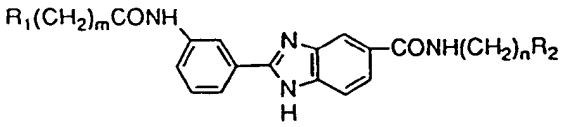
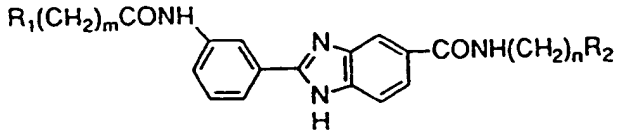
Compound No.	R_1	m	R_2	n
2061		1		0
2062		1		3
2063		1		0
2064		1		0
2065		1		0
2066		1		0
2067		1		3
2068		1		0
2069		1		0
2070		1		0

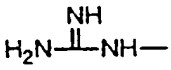
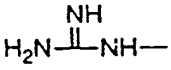
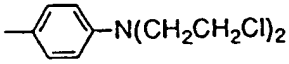
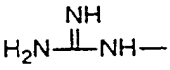
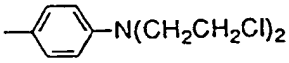
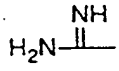
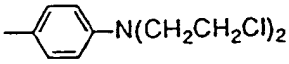
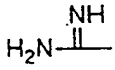
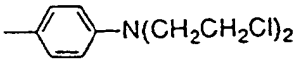
Table 1 (32)



Compound No.	R_1	m	R_2	n
2081	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	1	$-N(CH_2CH_2Cl)_2$	0
2082	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	1	$-N(CH_2CH_2Cl)_2$	3
2083	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	1	$-N(CH_2CH_2Cl)_2$, CH_3	0
2084	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	1	$-N(CH_2CH_2Cl)_2$, Cl	0
2085	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	1	$-N(CH_2CH_2Cl)_2$	0
2086	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	3	$-N(CH_2CH_2Cl)_2$	0
2087	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	3	$-N(CH_2CH_2Cl)_2$	3
2088	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	3	$-N(CH_2CH_2Cl)_2$, CH_3	0
2089	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	3	$-N(CH_2CH_2Cl)_2$, Cl	0
2090	$H_3C-\overset{CH_3}{\overset{\vert}{S}}{}^{+}-$	3	$-N(CH_2CH_2Cl)_2$	0

Table 1 (34)



Compound No.	R_1	m	R_2	n
2101		2		0
2102		4		0
2103		5		0
2104		1		0
2105		2		0

Reaction 2

1H-2-(3-nitrophenyl)benzimidazole-5-[N-(2-cyanoethyl)]carboxyamide

1.0 g (3.53 mmols) of 1H-2-(3-nitrophenyl)benzimidazole-5-carboxylic acid was suspended in 20 ml of DMF, and 0.69 g (4.26 mmols, 1.2 eq.) of CDI was then added, followed by stirring at room temperature in a nitrogen atmosphere. After 3.5 hours, the solution was cooled on ice. Then, 0.27 ml (3.65 mmols, 1.0 eq.) of β-aminopropionitrile was added to the solution, and the temperature of the solution was then returned to room temperature. After stirring for 3 hours, the solution was then allowed to stand overnight. Next, the solution was concentrated under reduced pressure, and the resulting residue was crystallized from methanol, thereby obtaining 1.08 g (3.19 mmols, 90.4%) of the desired compound in the state of ocher crystals.

mp: >270°C

NMR (DMSO-d_6) δ: 9.04 (s, 1H), 8.90 (m, 1H), 8.64 (d, 1H), 8.37 (d, 1H), 8.25-8.14 (m, 1H), 7.89 (t, 1H), 7.83-7.67 (m, 2H), 3.54 (q, 2H), 2.82 (t, 2H)

Reaction 3

1H-2-(3-nitrophenyl)benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride

1.08 g (3.22 mmols) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-(2-cyanoethyl)]carboxyamide was suspended in 40 ml of ethanol, and a hydrochloric acid gas was then blown into the suspension under ice cooling. After the suspension was saturated with a hydrochloric acid gas over 30 minutes, the temperature of the suspension was returned to room temperature, followed by stirring for 3 hours. Next, the suspension was concentrated under reduced pressure. The resulting residue was decanted twice with ether and then suspended in 40 ml of ethanol, and an ammonia gas was blown thereinto under ice cooling. After saturated with the ammonia gas over 50 minutes, the suspension was stirred at room temperature for 3 hours, and then allowed to stand overnight. Next, the suspension was concentrated under reduced pressure, and the resulting residue was then sludged with methanol/acetone. The resulting solid was purified through silica gel column chromatography (ethyl acetate/IPA/water = 5/2/1), and then sludged with methylene chloride and successively IPA to obtain 0.67 g (1.72 mmols, 53.5%) of the desired compound in the state of creamy crystals.

mp: >270°C

NMR (DMSO-d_6) δ: 9.10-9.06 (m, 3H), 8.88 (t, 0.5H), 8.79 (t, 0.5H), 8.71 (bs, 3H), 8.35 (d, 1H), 8.31 (s, 0.5H), 8.15 (s, 0.5H), 7.88 (t, 1H), 7.88 (d, 1H), 7.75 (d, 0.5H), 7.63 (d, 1H), 3.65 (q, 2H), 2.73 (t, 2H)

Reaction 4

1H-2-[3-[[4-[4-[N,N-bis(2-chloroethyl)amino]phenyl]butyryl]amino]phenyl]benzimidazole-5-[N-(2-amidinoethyl]carboxyamide hydrochloride

0.33 g (0.83 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride was suspended in a mixed solvent of DMF and methanol, and catalytic hydrogenation was then carried out in the presence of 10% Pd/C as a catalyst to lead the above-mentioned compound to a corresponding amino compound. This DMF solution was stirred under ice cooling and under a nitrogen gas stream, and a methylene chloride solution of 4-[4-[N,N-bis(2-chloroethyl)amino]phenyl]butyryl chloride {which was prepared by adding 0.55 g (4.6 mmols, 5.0 eq.) of thionyl chloride to 0.28 g (0.92 mmol) of chlorambucil, removing thionyl chloride under reduced pressure after 5 minutes, and then carrying out azeotropic distillation with benzene twice} was added dropwise. The temperature of the suspension was returned to room temperature, followed by stirring for 7 hours. Next, the suspension was concentrated under reduced pressure, and the resulting residue was then purified through silica gel column chromatography (ethyl acetate/IPA/water = 6/2/1), and then solidified with ethanol to obtain 0.23 g (0.36 mmols, 43.4%) of the desired compound in the state of light yellowish white crystals.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.31 (s, 1H), 9.09 (s, 2H), 8.98 (t, 1H), 8.68 (s, 1H), 8.66 (s, 2H), 8.27 (s, 1H), 7.97 (d, 2H), 7.78 (d, 1H), 7.70 (d, 1H), 7.58 (t, 1H), 7.07 (d, 2H), 6.68 (d, 2H), 3.65 (m, 2H), 2.72 (t, 2H), 2.55 (m, 2H), 2.40 (t, 2H), 1.89 (m, 2H)

IR (KBr) cm^{-1}: 3064, 1690, 1519, 1310, 1245, 810, 723

Next, the solution was stirred for 3 hours at room temperature and allowed to stand overnight. After concentration under reduced pressure, the resulting residue was sludged with methanol to obtain 0.47 g (1.4 mmols, 82.9%) of the desired compound in the state of yellow crystals.

mp: >270°C

NMR (DMSO-d_6) δ: 8.94-8.9 (m, 1H), 8.45 (s, 4H), 8.3 (s, 0.5H), 8.1 (s, 0.5H), 7.85 (d, 0.5H), 7.65 (d, 0.5H), 3.54 (q, 2H), 2.82 (t, 2H)

Reaction 5

1H-2-(4-nitrophenyl)benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride

In 10 ml of ethanol was suspended 0.47 g (1.4 mmols) of 1H-2-(4-nitrophenyl)benzimidazole-5-[N-(2-cyanoethyl)]carboxyamide, and a hydrochloric acid gas was blown into the suspension over 30 minutes under ice cooling to saturate the suspension with the gas. Afterward, the suspension was stirred at room temperature for 2 hours to precipitate a solid after it was once dissolved. After concentration under reduced pressure, the resulting residue was sludged with ether, collected by filtration, and then suspended in 15 ml of ethanol. Next, an ammonia gas was blown into the suspension over 2 hours to saturate it with the gas, whereby a solid was precipitated after it was once dissolved. The reaction system was allowed to stand overnight, as it was. Next, methanol and acetone were added to the reaction solution, and the undissolved precipitate was collected by filtration to obtain 0.42 g (1.1 mmols, 77.9%) of the desired compound in the state of yellow crystals.

mp: >279°C

NMR (DMSO-d_6) δ: 9.5 (bs, 3H), 8.83 (m, 1H), 8.5 (d, 2H), 8.43 (s, 1H), 8.24 (s, 1H), 7.83 (d, 1H), 7.7 (d, 1H), 3.65 (m, 2H), 2.72 (t, 2H)

Reaction 6

1H-2-[4-[[4-[4-[N,N-bis(2-chloroethyl)amino]phenyl]butyryl]amino]phenyl]benzimidazole-5-[N-(2-amidinoethyl]carboxyamide hydrochloride

0.24 g (3.3 mmols) of thionyl chloride was added to 0.12 g (0.39 mmol) of chlorambucil, and the mixture was then stirred at room temperature for 5 minutes. Next, thionyl chloride was distilled off under reduced pressure and further removed by doing azeotropic distillation with benzene twice, and methylene chloride was then added. This solution was added to a DMF solution containing 0.54 mmol of 1H-2-(4-aminophenyl)benzimidazole-5-[N-(2-amidinoethyl]carboxyamide hydrochloride (which was obtained by subjecting the nitro compound of Reaction 5 to catalytic hydrogenation using 10% Pd/C as a catalyst) under ice cooling, and the solution was stirred at room temperature for 5 hours and then allowed to stand overnight. Next, a formed solid was removed by filtration, and the filtrate was then concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (methylene chloride/methanol/acetic acid = 80/20/1), and then crystallized from ether, thereby obtaining 71 mg (0.11 mmols, 20.4%) of the desired compound in the state of light brown crystals.

mp: Decomposed from 209°C

NMR (DMSO-d_6) δ: 10.4 (s, 1H), 9.07 (s, 2H), 8.97 (m, 1H), 8.64 (s, 2H), 8.29 (d, 2H), 8.24 (s, 1H), 7.95 (d, 1H), 7.87 (d, 2H), 7.77 (d, 1H), 7.07 (d, 2H), 6.67 (d, 2H), 3.70 (s, 8H), 3.64 (m, 2H), 2.71 (m, 2H), 2.39 (m, 2H), 1.88 (m, 2H)

IR (KBr) cm^{-1}: 3100, 1686, 1519, 1322, 1258, 1193, 843, 740

Elemental analysis: ($C_{31}H_{35}Cl_2N_7O_2 \cdot 2HCl \cdot 3H_2O$)				
Calcd.:	C:50.62,	H:5.89,	N:13.33,	Cl:19.28
Found:	C:50.68,	H:5.48,	N:13.63,	Cl:18.88

Example 4 (Compound 45)

2-[4-(formylamino)phenyl]benzimidazole-5-[N-(2-amidinoethyl]carboxyamide hydrochloride

Reaction 1

1H-2-(4-aminophenyl)benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride

In a mixed solvent of 4 ml of DMF and 4 ml of methanol was dissolved 0.42 g (1.08 mmols) of 1H-2-(4-nitrophenyl)benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride, and catalytic hydrogenation was then carried out by using 0.18 g of 10% Pd/C as a catalyst. After the removal of the catalyst, methanol was distilled off, and the half of the solution containing DMF was taken out and used in the next reaction.

Reaction 2

1H-2-[4-(formylamino)phenyl]benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride

A solution, which had been prepared by adding 0.10 ml (2.65 mmols) of formic acid to 4 ml of a THF solution containing 0.44g (2.7 mmols) of CDI and then stirring the solution at room temperature for 30 minutes under a nitrogen gas stream, was added dropwise to a DMF solution containing 0.54 mmol of 1H-2-(4-aminophenyl)benzimidazole-5-[N-(2-amidinoethyl)]carboxyamide hydrochloride under ice cooling under a nitrogen gas stream with stirring. Afterward, the temperature of the solution was returned to room temperature, followed by stirring for 6.5 hours. Next, the solution was concentrated under reduced pressure, and the resulting residue was purified through reversed phase silica gel column chromatography (ODS, water/methanol = 50%), and then crystallized from ethanol-ether to obtain 36 mg (0.093 mmol, 17.2%) of the desired compound in the state of white crystals.

mp: 220-229°C

NMR (DMSO-d_6, 80°C) δ: 10.80 (s, 1H), 9.06 (bs, 2H), 8.80 (bs, 3H), 8.40 (s, 1H), 8.17 (d, 1H), 8.12 (s, 1H), 7.93 (d, 2H), 7.72 (d, 1H), 6.83 (d, 2H), 3.45 (m, 2H), 2.44 (m, 2H)

IR (KBr) cm^{-1}: 3422, 1648, 1606, 1499, 1400, 1195, 840

Example 5 (Compound 44)

1H-2-[4-(formylamino)phenyl]benzimidazole-5-[N-[3-(dimethylamino)propyl]]carboxyamide

Reaction 1

1H-2-(4-nitrophenyl)benzimidazole-5-[N-[3-(dimethylamino)propyl]]carboxyamide

In 50 ml of DMF was dissolved 0.50 g (1.77 mmols) of 1H-2-(4-nitrophenyl)benzimidazole-5-carboxylic acid, and 0.34 g (2.1 mmols, 1.2 eq.) of CDI was added, followed by stirring at room temperature in a nitrogen atmosphere. After 4 hours, the solution was cooled on ice. Then, 0.24 ml (1.9 mmols, 1.1 eq.) of N,N-dimethyl-1,3-propanediamine was added to the solution, and the temperature of the solution was returned to room temperature and the solution was then allowed to stand overnight. After the completion of the reaction had been confirmed, the solution was concentrated under reduced pressure, and the resulting residue was sludged with methanol to obtain 0.52 g (1.42 mmols, 80.2%) of the desired compound in the state of yellowish white crystals.

mp: 261-265°C

NMR (DMSO-d_6) δ: 8.57 (t, 1H), 8.45 (s, 4H), 8.17 (s, 1H), 7.80 (d, 1H), 7.71 (d, 1H), 3.33 (q, 2H), 2.30 (t, 2H), 1.70 (m, 2H)

Reaction 2

1H-2-[4-(formylamino)phenyl]benzimidazole-5-[N-[3-(dimethylamino)propyl]]carboxyamide

In a mixed solvent of 6 ml of DMF and 4 ml of methanol was suspended 0.18 g (0.49 mmol) of 1H-2-(4-nitrophenyl)benzimidazole-5-[N-[3-(dimethylamino)propyl]]carboxyamide, and catalytic hydrogenation was then carried out by the use of 10% Pd/C as a catalyst to lead it to a corresponding amino compound. This compound was dissolved in 8 ml of DMF and then ice-cooled, and a formylimidazole/ THF solution [0.38 g (2.34 mmols) of CDI, prepared from 88 µl of formic acid and 4 ml of THF] was added dropwise under a nitrogen gas stream. Next, the temperature of the solution was returned to room temperature, and the solution was stirred for 7.5 hours and then allowed to stand overnight. After

Example 7 (Compound 1001)

1H-2-[4-(guanidinoacetylamino)phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide dihydrochloride

Reaction 1

1H-2-(4-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis (2-chloroethyl)amino]phenyl]]carboxyamide

In 8 ml of DMF were suspended 0.26 g (0.96 mmol) of 1H-2-(4-nitrophenyl)benzimidazole-5-carboxylic acid and 0.27 g (0.95 mmol) of N,N-bis(2-chloroethyl)-1,4-phenylenediamine hydrochloride, and the solution was then stirred under a nitrogen gas stream, while cooled on ice. Next, 0.40 ml (2.87 mmols, 3.0 eq.) of triethylamine and 0.22 ml (1.45 mmols, 1.5 eq.) of DECP were added in this order, and the solution was stirred for 3 hours and then allowed to stand overnight, as it was. After concentration under reduced pressure, the resulting residue was sludged with methanol to obtain 0.33 g (0.66 mmol, 69.7%) of the desired compound in the state of light brown crystals.

mp: >250°C

NMR (DMSO-d_6) δ: 10.11 (s, 0.5H), 10.05 (s, 0.5H), 8.46 (s, 4H), 8.42 (s, 0.5H), 8.17 (s, 0.5H), 7.95-7.84 (m, 1.5H), 7.68 (d, 0.5H), 6.77 (d, 2H), 6.64 (d, 2H), 3.74 (s, 8H)

Reaction 2

1H-2-[4-(guanidinoacetylamino)phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide dihydrochloride

0.12 ml of 1N hydrochloric acid was added to a solution conposed of a mixed solvent of DMF and methanol and 50 mg (0.10 mmol) of 1H-2-(4-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide. Then the mixture was subjected to catalytic hydrogenation in the presence of 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 20 µl (0.14 mmol, 1.4 eq.) of triethylamine, 46 mg (0.30 mmol, 3.0 eq.) of guanidineacetic acid hydrochloride and 62 mg (0.30 mmol, 3.0 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 2 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was then concentrated under reduced pressure. The resulting residue was subjected to gel filtration (Sephadex LH-20, methanol), and 4N hydrochloric acid and dioxane were added to the eluted fraction. Next, the solution was concentrated and then sludged with methanol to obtain 10 mg (0.016 mmol, 15.6%) of the desired compound in the state of white crystals.

mp: 215-227°C (decomposed)

NMR (DMSO-d_6) δ: 10.30 (s, 1H), 8.35 (d, 2H), 8.32 (s, 1H), 8.05 (d, 1H), 7.93 (d, 2H), 7.83 (d, 1H), 7.63 (d, 3H), 7.50-7.20 (bs, 4H), 6.78 (d, 2H), 4.16 (d, 2H), 3.74 (s, 8H)

IR (KBr) cm^{-1}: 3332, 1652, 1602, 1516, 1328, 737

Example 8 (Compound 1010)

1H-2-[4-(guanidinoacetylamino)phenyl]benzimidazole-5-[N-[3-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide

Reaction 1

m-[N,N-bis(2-hydroxyethyl)amino]nitrobenzene

In 36 ml of 30% acetic acid was dissolved 5.0 g (36.2 mmols) of m-aminonitrobenzene, and 22.9 ml of ethylene oxide was further added under ice cooling, followed by stirring at room temperature overnight. After extraction with ethyl acetate, the ethyl acetate layer was dried over sodium sulfate and concentrated. The resulting residue was sludged with ether to obtain 5.21 g (23.0 mmols, 63.6%) in the state of yellow crystals.

mp: 98.5-100°C

NMR (DMSO-d_6) δ: 7.51 (d, 1H), 7.51 (s, 1H), 7.32 (t, 1H), 6.99 (d, 1H), 3.89 (t, 4H), 3.73 (bs, 2H), 3.65 (t, 4H)

mp: 200-210°C

NMR (DMSO-d_6) δ: 10.27 (s, 1H), 9.41 (s, 1H), 8.33 (d, 2H), 8.30 (s, 1H), 7.96 (d, 1H), 7.90 (d, 2H), 7.80 (d, 1H), 7.64 (t, 1H), 7.50-7.15 (m, 7H), 6.51 (d, 1H), 4.16 (d, 2H), 3.76 (m, 8H)

IR (KBr) cm^{-1}: 3339, 1654, 1604, 1542

Example 9 (Compound 2001)

1H-2-[3-(guanidinoacetylamino)phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide dihydrochloride

Reaction 1

1H-2-(3- nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide

In 12 ml of DMF were dissolved 0.30 g (1.06 mmols) of 1H-2-(3-nitrophenyl)benzimidazole-5-carboxylic acid and 0.29 g (1.08 mmols, 1.0 eq.) of N,N-bis(2-chloroethyl)-1,4-phenylenediamine hydrochloride, and the solution was then stirred under a nitrogen gas stream while cooled on ice. Next, 0.45 ml (3.23 mmols, 3.0 eq.) of triethylamine and 0.24 ml (1.58 mmols, 1.5 eq.) of DECP were added in this order, and the solution was stirred for 3 hours and then allowed to stand overnight, as it was. After concentration under reduced pressure, methanol was added to the resulting residue, and the solution was then allowed to stand for 3 hours. Next, the resulting solid was collected by filtration to obtain 0.45 g (0.90 mmol, 85.2%) of the desired compound in the state of ocherous powder.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.06 (bs, 1H), 9.06 (s, 1H), 8.66 (d, 1H), 8.38 (d, 1H), 8.38 (s, 0.5H), 8.16 (s, 0.5H), 7.90 (t, 1H), 7.93-7.70 (m, 2H), 7.63 (d, 2H), 6.77 (d, 2H), 3.74 (s, 8H)

Reaction 2

1H-2-[3-(guanidinoacetylamino)phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide dihydrochloride

In DMF-methanol, 0.15 g (0.30 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.14 g (0.91 mmols, 3.0 eq.) of guanidineacetic acid hydrochloride and 0.19 g (0.92 mmol, 3.0 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 9 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was concentrated under reduced pressure. Next, the residue was subjected to gel filtration (Sephadex LH-20, methanol), and 4N hydrochloric acid and dioxane were added to the eluted fraction, followed by concentration. The concentrated solution was crystallized from methanol, thereby obtaining 0.13 g (0.20 mmol, 67.7%) of the desired compound in the state of light yellowish white crystals.

mp: >250°C

NMR (DMSO-d_6) δ: 10.71 (s, 1H), 10.23 (s, 1H), 8.65 (s, 1H), 8.31 (s, 1H), 8.01 (d, 2H), 7.82-7.77 (m, 2H), 7.64 (m, 4H), 7.60-7.20 (bs, 4H), 6.77 (d, 2H), 4.16 (d, 2H), 3.74 (s, 8H)

IR (KBr) cm^{-1}: 3310, 1652, 1517

Elemental analysis: ($C_{27}H_{28}Cl_2N_8O_2 \cdot 2HCl \cdot H_2O$)				
Calcd.:	C:49.25,	H:4.90,	N:17.02,	Cl:21.54
Found:	C:49.30,	H:4.70,	N:16.91,	Cl:21.61

and therefore, together with the resulting filtrate, the crystals were subjected to gel filtration (Sephadex LH-20, methanol). Next, solidification was accomplished with ether, thereby obtaining 0.48 g (0.90 mmol, 42.0%) of the desired compound in the state of ocherous solid.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.39 (s, 1H), 9.06 (s, 1H), 8.66 (d, 1H), 8.38 (d, 1H), 8.32 (s, 1H), 8.03 (d, 1H), 7.93-7.87 (m, 2H), 7.76 (d, 1H), 7.73 (dd, 1H), 7.37 (d, 1H), 3.64-3.48 (m, 8H)

Reaction 2

1H-2-[3-(guanidinoacetylamino)phenyl]benzimidazole-5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino] phenyl]]carboxyamide dihydrochloride

In DMF-methanol, 0.21 g (0.40 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.18 g (1.17 mmols, 3.0 eq.) of guanidineacetic acid hydrochloride and 0.24 g (1.16 mmols, 3.0 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 2 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was concentrated under reduced pressure. Next, the residue was subjected to gel filtration (Sephadex LH-20, methanol), and 4N hydrochloric acid and dioxane were added to the eluted fraction, followed by concentration. The concentrated material was solidified with ether, thereby obtaining 0.15 g (0.22 mmol, 55.7%) of the desired compound in the state of light yellowish white power.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.78 (s, 1H), 10.63 (s, 1H), 8.67 (s, 1H), 8.37 (s, 1H), 8.04 (m, 2H), 7.88-7.63 (m, 5H), 7.60-7.25 (bs, 4H), 7.37 (d, 1H), 4.18 (d, 2H), 3.62 (t, 4H), 3.51 (t, 4H)

IR (KBr) cm^{-1}: 3313, 1673, 1498, 1385, 1307, 1252

Elemental analysis: ($C_{27}H_{27}Cl_3N_8O_2 \cdot 2HCl \cdot 5H_2O$)			
Calcd.:	C:42.40,	H:5.14,	N:14.65
Found:	C:42.48,	H:4.73,	N:14.67

Example 12 (Compound 2011)

1H-2-[3-[[4-(guanidino)butyryl]amino]phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino)phenyl]]carboxyamide dihydrochloride

In DMF-methanol, 0.20 g (0.40 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.22 g (1.21 mmols, 3.0 eq.) of guanidinobutyric acid hydrochloride and 0.25 g (1.21 mmols, 3.0 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 3 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was concentrated under reduced pressure. Next, the residue was purified through silica gel column chromatography (ethyl acetate/IPA/water = 6/2/1) and then subjected to gel filtration (Sephadex LH-20, methanol), and 4N hydrochloric acid and dioxane were added to the eluted fraction, followed by concentration. The concentrated material was solidified with ether, thereby obtaining 0.10 g (0.15 mmol, 37.5%) of the desired compound in the state of yellow power (hygroscopic).

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.59 (s, 1H), 10.32 (s, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 8.10 (d, 1H), 8.05 (d, 1H), 7.95 (t, 1H), 7.87 (d, 1H), 7.79 (d, 1H), 7.65 (m, 3H), 7.50-7.00 (bs, 4H), 6.77 (d, 2H), 3.74 (s, 8H), 3.18 (q, 2H), 1.85 (m, 2H)

IR (KBr) cm^{-1}: 3164, 1655, 1517, 1330, 1247, 1182

Elemental analysis: ($C_{29}H_{31}Cl_3N_8O_2 \cdot 2HCl \cdot 0.5H_2O$)			
Calcd.:	C:48.93,	H:4.81,	N:15.74
Found:	C:48.65,	H:5.16,	N:15.65

Example 15 (Compound 2031)

1H-2-[3-[[4-(dimethylamino)butyryl]amino]phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide dihydrochloride

In DMF-methanol, 0.20 g (0.40 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.20 g (1.19 mmols, 3.0 eq.) of 4-dimethylaminobutyric acid hydrochloride and 0.25 g (1.21 mmols, 3.0 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 4.5 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was concentrated under reduced pressure, and the resulting residue was then purified through silica gel column chromatography (ethyl acetate/IPA/water = 5/2/1) and then further subjected to gel filtration (Sephadex LH-20, methanol). Since the presence of impurities was observed, the solution was subjected to silica gel column chromatography (ethyl acetate/methanol = 1/1) again and then further subjected to gel filtration (Sephadex LH-20, methanol). Next, solidification was carried out with ether to obtain 89 mg (0.14 mmol, 34.0%) of the desired compound in the state of a light yellowish white solid.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.25 (s, 1H), 10.07 (s, 0.5H), 10.01 (s, 0.5H), 8.59 (s, 0.5H), 8.57 (s, 0.5H), 8.33 (s, 0.5H), 8.12 (s, 0.5H), 7.88-7.48 (m, 7H), 6.77 (d, 2H), 3.74 (s, 8H), 2.75 (m, 2H), 2.54 (s, 6H), 2.45 (s, 6H), 1.90 (m, 2H)

IR (KBr) cm^{-1}: 3214, 1614, 1518, 1328, 1244, 1182

Elemental analysis: ($C_{30}H_{34}Cl_2N_6O_2 \cdot HCl \cdot H_2O$)			
Calcd.:	C:56.65,	H:5.86,	N:13.21
Found:	C:56.60,	H:5.78,	N:13.00

Example 16 (Compound 2091)

1H-2-[3-[[3-(methylthio)propionyl]amino]phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide

In a mixed solvent of 5ml of DMF and 3ml of methanol, 0.27 g (0.54 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 70 µl (0.68 mmol, 1.25 eq.) of 3-(methylthio)propionic acid and 0.13 g (0.63 mmol, 1.2 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 2.5 hours and then allowed to stand overnight. Since the progress of the reaction stopped the next day, 70 µl (0.68 mmol) of 3-(methylthio)propionic acid and 0.13 g (0.63 mmol) of DCC were added, and the solution was stirred for 10 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was concentrated under reduced pressure, and the resulting residue was then purified through silica gel column chromatography (chloroform/methanol = 4%) and then crystallized from ether, thereby obtaining 0.17 g (0.30 mmol, 55.2%) of the desired compound in the state of light yellowish white crystals.

Example 19 (Compound 2044)

2-[N-[3-[5-[N-[3-methyl-4-[N,N-bis(2-chloroethyl)amino]phenyl]carbamoyl]-1H-benzimidazole-2-yl]phenyl]]carbamoylethyl-dimethylsulfonium iodide

0.10 g (0.17 mmol) of 1H-2-[3-[[3-(methylthio)propionyl]amino]phenyl]benzimidazole-5-[N-[3-methyl-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was dissolved in a mixture of 0.6 ml of 80% formic acid, 0.3 ml of acetic acid and 0.5 ml of methyl iodide, and the solution was then stirred at room temperature for 3 hours under shading and then allowed to stand overnight. After concentration under reduced pressure, the resulting residue was purified through gel filtration column chromatography (Sephadex LH-20, methanol, carried out twice). The solvents were distilled off under reduced pressure, and the resulting residue was dissolved in methanol. Afterward, IPA was added to the solution, so that precipitation occurred again, thereby obtaining 58 mg (yield = 47%) of the desired compound in the state of light yellow powder.

NMR (DMSO-d_6) δ: 10.56 (s, 1H), 10.20 (s, 1H), 8.59 (s, 1H), 8.27 (s, 1H), 7.91 (d, 2H), 7.78-7.55 (m, 5H), 7.24 (d, 1H), 3.57 (t, 4H), 3.37 (t, 4H), 3.21 (t, 2H), 3.05 (t, 2H), 2.97 (s, 6H), 2.31 (s, 3H)

IR (KBr) cm-1: 3422, 1654, 1502, 1313, 1118, 885

Example 20 (Compound 2093)

1H-2-[3-[3-(methylthio)propionylamino]phenyl]benzimidazole-5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide

In DMF-methanol, 0.21 g (0.40 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.12 ml (1.16 mmols, 2.9 eq.) of 3-methylthiopropionic acid and 0.24 g (1.16 mmols, 2.9 eq.) of DCC were added in this order. Afterward, the temperature of the solution was returned to room temperature, and the solution was stirred for 2 hours and then allowed to stand overnight. After the removal of a formed solid by filtration, the filtrate was concentrated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (chloroform/ methanol = 4%) and then solidified with ether, thereby obtaining 0.18 g (0.30 mmol, 75.3%) of the desired compound in the state of light yellowish white powder.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.36 (s, 1H), 10.23 (s, 1H), 8.58 (s, 1H), 8.25 (s, 1H), 8.02 (d, 1H), 7.85 (d, 2H), 7.75-7.69 (m, 2H), 7.52 (t, 1H), 7.37 (d, 1H), 3.62 (t, 4H), 3.50 (t, 4H), 2.80 (t, 2H), 2.68 (t, 2H)

Example 21 (Compound 2046)

2-[N-[3-[5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino]phenyl]carbamoyl]-1H-benzimidazole-2-yl]phenyl]carbamoylethyl]dimethylsulfonium iodide

0.10 g (0.17 mmol) of 1H-2-[3-(3-methylthiopropionylamino)phenyl]benzimidazole-5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was dissolved in a mixture of 0.5 ml of 85% formic acid and 0.25 ml of acetic acid, and 0.2 ml of methyl iodide was then added, followed by stirring at room temperature for 3 days under shading. After concentration under reduced pressure, the resulting residue was subjected to gel filtration (Sephadex LH-20, methanol), and then solidified with ether, thereby obtaining 0.10 g (0.13 mmol, 81.2%) of the desired compound in the state of light yellowish white powder.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.48 (s, 1H), 10.35 (s, 1H), 8.58 (s, 1H), 8.25 (s, 1H), 8.02 (s, 1H), 7.86 (m, 2H), 7.71 (m, 3H), 7.55 (t, 1H), 7.36 (d,1H), 3.64-3.48 (m, 8H), 3.03 (t, 2H), 2.97 (s, 6H)

IR (KBr) cm^{-1}: 3248, 1655, 1577, 1497, 1389, 1307

then sludged with ether/chloroform to obtain 0.25 g (0.38 mmol, 38.0%) of the desired compound in the state of white powder.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.25 (s, 1H), 10.18 (s, 0.5H), 10.13 (s, 0.5H), 8.55 (d, 1H), 3.34 (s, 0.5H), 8. 12 (s, 0.5H), 7.88-7.48 (m, 7H), 7.24 (d, 1H), 3.61-3.50 (m, 8H), 3.64 (t, 4H), 2.67 (t, 2H), 2.54 (t, 2H), 2.43 (bs, 4H), 2.31 (s, 3H)

IR (KBr) cm^{-1}: 3258, 2963, 1648, 1502, 1446, 1314, 1115

Example 24 (Compound 2054)

1H-2-[3-[(3-morpholinopropionyl)amino]phenyl]benzimidazole-5-[N-[3-chloro-4-[N-bis(2-chloroethyl)amino]phenyl]]carboxyamide hydrochloride

In DMF-methanol, 0.30 g (0.56 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[3-chloro-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.16 ml (1.15 mmols, 2.0 eq.) of triethylamine and a chloroform solution containing 1.13 mmols of 3-morpholinopropionyl chloride {which was prepared from 0.22 g (1.13 mmols) of 3-morpholinopropionic acid and 1 ml of thionyl chloride in chloroform} were added in this order. Afterward, the temperature of the solution was returned to room temperature, followed by stirring. After 3 hours, 0.16 ml (1.15 mmols) of triethylamine and the chloroform solution containing 1.13 mmols of 3-morpholinopropionyl chloride were further added, and the solution was then allowed to stand overnight. After concentration under reduced pressure, the resulting residue was subjected to silica gel column chromatography (chloroform/methanol = 12%). The eluted fraction was further subjected to gel filtration (Sephadex LH-20, methanol), and 4N hydrochloric acid and dioxane were added, followed by concentration. Next, solidification was accomplished with a small amount of ethanolether, thereby obtaining 0.13 g (0.18 mmol, 32.4%) of the desired compound in the state of light yellowish white amorphous powder.

mp: A definite melting point was not present.

NMR (DMSO-d_6) δ: 10.80 (s, 1H), 10.61 (s, 1H), 8.62 (s, 1H), 8.37 (s, 1H), 8.04 (m, 3H), 7.87-7.73 (m, 3H), 7.64 (t, 1H), 7.37 (d, 1H), 3.87-3.79 (m, 4H), 3.62 (t, 4H), 3.51 (t, 4H), 3.44 (m, 4H), 3.06 (m, 4H)

IR (KBr) cm^{-1}: 3214, 1671, 1576, 1497, 1394, 1307, 1128, 1087

Elemental analysis: ($C_{31}H_{33}Cl_3N_6O_3 \cdot HCl \cdot 6.5H_2O$)			
Calcd.:	C:46.69,	H:5.94,	N:10.54
Found:	C:46.53,	H:5.95,	N:10.45

Example 25 (Compound 2061)

1H-2-[3-(3-pyridylacetylamino)phenyl]benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]carboxyamide

In DMF-methanol, 0.40 g (0.80 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.21 g (1.21 mmols, 1.5 eq.) of 3-pyridylacetic acid hydrochloride and 0.23 g (1.20 mmols, 1.5 eq) of EDCI were added in this order. Afterward, the temperature of the solution was returned to room temperature, followed by stirring for 2.5 hours. After concentration under reduced pressure, the resulting residue was subjected to silica gel column chromatography (chloroform/methanol = 8%), and then solidified with ether. Since some impurities were contained in the powder, a separating operation was carried out by the use of chloroform and dilute ammonia water to precipitate insolubles. Next, the insolubles were collected by filtration to obtain 49 mg (0.083 mmol, 10.4%) of the desired compound in the state of light brown solid. Furthermore, the resulting chloroform layer was concentrated, and then solidified with ether, thereby obtaining 65 mg (0.10 mmol, 12.5%) of the desired hydrochloride in the state of light brown powder.

mp: A definite melting point was not present.

Free form: NMR (DMSO-d_6) δ: 10.47 (s, 1H), 10.00 (s, 0.5H), 8.57 (s, 1H), 8.55 (d, 1H), 8.48 (d, 1H), 8.32 (s, 0.5H), 8.10 (s, 0.5H), 7.87-7.49 (m, 8H), 7.38 (t, 1H), 6.77 (d, 2H), 3.77 (s, 2H), 3.73 (s, 8H)

Example 28 (Compound 2073)

1H-2-[3-(4-pyridylacetylamino)phenyl]benzimidazole-5-[N-[3-methyl-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide

In 10 ml of a mixed solvent of DMF:methanol = 1:1, 0.40 g (0.80 mmol) of 1H-2-(3-nitrophenyl)benzimidazole-5-[N-[3-methyl-4-[N,N-bis(2-chloroethyl)amino]phenyl]]carboxyamide was subjected to catalytic hydrogenation using 10% Pd/C as a catalyst to lead it to a corresponding amino compound. Next, the DMF solution of this amino compound was stirred under a nitrogen gas stream while cooled on ice, and 0.4 g (2.3 mmols, 3 eq.) of 4-pyridylacetic acid hydrochloride and 0.45 g (2.4 mmols, 3 eq) of EDCI were added in this order, followed by stirring for 30 minutes as it was. After stirred at room temperature for additional 6 hours, the solution was allowed to stand overnight. After the solvents were distilled off under reduced pressure, the resulting residue was purified through silica gel column chromatography (chloroform/methanol = 6/1). The solvents were distilled off, and the residue was further purified through silica gel column chromatography (chloroform/methanol = 8/1). The solvents were distilled off, and the residue was then dissolved in methanol. Next, isopropyl ether was added, so that precipitation occurred again, to obtain 50 mg (yield = 11%) of light yellow powder.

NMR (DMSO-d_6) δ: 10.51 (s, 1H), 10.18 (bs, 0.5H), 10.13 (bs, 0.5H), 8.61 (s, 1H), 8.55 (d, 2H), 8.33 (s, 0.5H), 8.11 (s, 0.5H), 7.89-7.49 (m, 7H), 7.39 (d, 2H), 7.23 (d, 1H), 3.77 (s, 2H), 3.57 (t, 4H), 3.36 (t, 4H), 2.31 (s, 3H)

IR (KBr) cm^{-1}: 3422, 1647, 1508, 1318, 1239, 829

Formulation Example 1

Compound No. 2053 as an active ingredient	30 g
Lactose	68 g
Crystalline cellulose	20 g
Magnesium stearate	2 g

The components described above are mixed in the above composition and the resulting mixture was formulated into core tablets by a tableting machine. Each of the core tablets weighed 120 mg containing 30 mg of Compound No. 2053 and had a diameter of 7 mm.

Talc was then sprinkled on each core tablet and the surface having talc was then coated with varnish to form an undercoat. Additional varnish coating was repeated so as to obtain tablets suitable for the internal uses. Color coating was further conducted. After drying, the tablets having the color coats were waxed and polished into tablets of uniform gloss.

Formulation Example 2

As an active ingredient, 1 g of Compound No. 2053 was weighed and dissolved in 1,000 ml of sterilized propylene glycol. The resting solution was poured and enclosed in ampoules so as to obtain injections in ampoules, each of which contained 5 ml of the solution.

Test Example 1

Investigation was made on the linkage of each compound to DNA. The test was carried out by comparing a Tm value in the case that the compound was added to the DNA solution with a Tm value in the case that no compound was added thereto.

That is to say, poly d(A-T)-d(A-T) was used as the DNA. This DNA was dissolved in a buffer solution and the compound was further added thereto, and the Tm value was then measured. On the other hand, the Tm of the DNA alone was measured, and a difference (ΔTm) was then calculated. For the measurement, a U-3200 model spectrophotometer made by Hitachi, Ltd. was used, and for the control of temperature, SPR-10 model made by Hitachi, Ltd. was used.

The ΔTm of Compound 2001 was obtained, and it was 14°C.

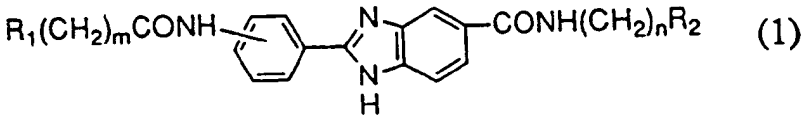
Table 3 shows the results of the test. The T/C values correspond to compound numbers, respectively, and each value in the parentheses represents the concentration of the drug at the time when its T/C value was obtained.

Table 3

Compound No.	T/C (%)	Dose (mg/kg)
2001	13	30
2006	21	10
Adriamycin	29	20

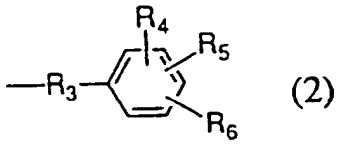
Claims

1. A compound represented by the following formula (1) or its pharmacologically acceptable salt:



(1)

wherein each of m and n is independently an integer of from 0 to 5; each of R_1 and R_2 is independently a hydrogen atom, a halogen atom, an alkylthio group having 1 to 8 carbon atoms, an amino group which may be substituted, an ammonium group which may be substituted, a sulfonium group which may be substituted, a phenyl group which may be substituted, a hetero-five-membered ring group which may be substituted, a hetero-six-membered ring group which may be substituted, an amidino group, a guanidino group, an amino acid residue or a group represented by the formula (2)



(2)

wherein R_3 is a direct bond or an oxygen atom {when R_3 is an oxygen atom, m or n of $(CH_2)_m$ or $(CH_2)_n$ to which R_3 bonds is not 0}; R_4 is a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, an alkoxy group having 1 to 8 carbon atoms, a halogen atom, a trifluoromethyl group, a cyano group, an amidino group, a carboxyl group or -COR_7 wherein R_7 is an alkylamino group having 1 to 8 carbon atoms which may be substituted by a substituted amino group, an amino group which may be substituted by a phenyl group which may be substituted, or a benzylamino group which may be substituted; R_5 is a hydrogen atom, an alkyl group having 1 to 8 carbon atoms, an alkoxy group having 1 to 8 carbon atoms or a halogen atom; R_6 is a -$(CH_2)_pN(R_8)_2$ or -$(CH_2)_pNR_8R_9$ wherein p is an integer of from 0 to 5; R_8 is -CH_2CH_2W wherein W is a halogen atom, a hydroxyl group, a mesyloxy group or a tosyloxy group or -$OCOR_7$ wherein R_7 is as defined above; R_9 is an alkyl group having 1 to 5 carbon atoms or a mesyl group;

the phenyl group having a $R_1(CH_2)_mCONH$ group in formula (1) can be substituted by the $R_1(CH_2)_mCONH$ group at any position.
position of the phenyl group.

2. The compound or its pharmacologically acceptable salt according to claim 1 wherein R_1 and/or R_2 is an alkylthio group having 1 to 4 carbon atoms.

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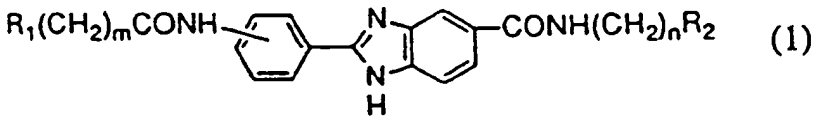
(71) Applicant: **MITSUI TOATSU CHEMICALS, INC.**
Tokyo (JP)

(72) Inventors:
- **Matsunaga, Akio**
  Mobara-shi, Chiba-ken (JP)
- **Nakajima, Yuki**
  Mobara-shi, Chiba-ken (JP)
- **Kohno, Hiroshi**
  Mobara-shi, Chiba-ken (JP)
- **Ohkouchi, Hiroshi**
  Mobara-shi, Chiba-ken (JP)
- **Iwata, Daiji**
  Mobara-shi, Chiba-ken (JP)
- **Edatsugi, Hajime**
  Mobara-shi, Chiba-ken (JP)

(74) Representative: **VOSSIUS & PARTNER**
Siebertstrasse 4
81675 München (DE)

(54) Phenylbenzimidazole derivatives

(57) An anticancer agent, an antiviral agent or an antimicrobial agent which contains, as an active ingredient for acting on DNA, a compound presented by the following formula (1) or its pharmacologically acceptable salt:



(1)

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EUROPEAN SEARCH REPORT

Application Number
EP 95 12 0576

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A,D	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, 1989, pages 774-8, XP000608784 F. M. ARCAMONE ET AL.: "Synthesis, DNA-Binding Properties, and Antitumor Activity of Novel Distamycin Derivatives" ---	1	
A	EP-A-0 194 529 (GÖDECKE AG) * claim 1 * ---	1,9	
A	EP-A-0 148 431 (DR. KARL THOMAE GMBH) * claim 1 * ---	1	
A	EP-A-0 209 707 (DR. KARL THOMAE GMBH) * claim 1 * -----	1	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	11 December 1996	Hass, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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